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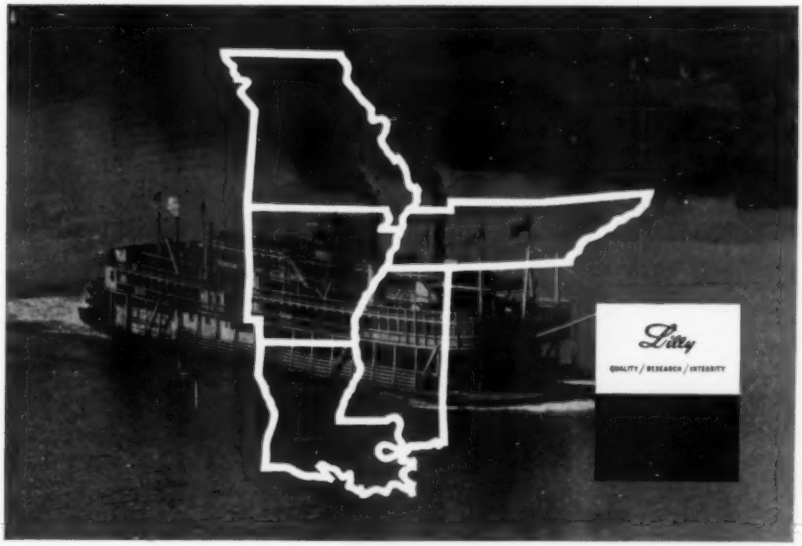

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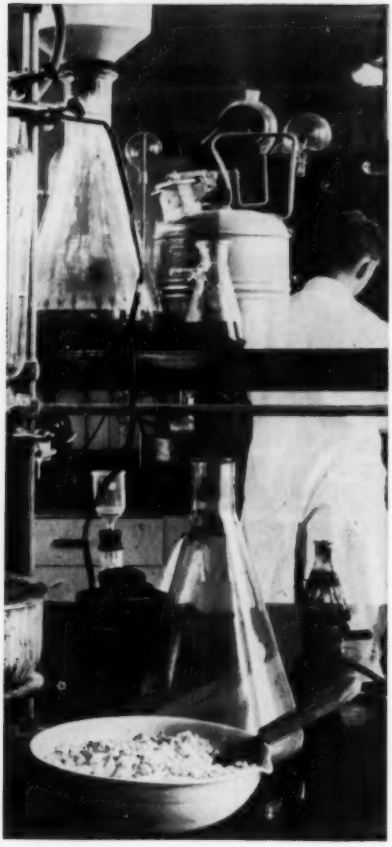

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E D I T O R I A L

THE A. PH. A. LABORATORY

THE concept of a laboratory functioning as a part of the activities of the A. Ph. A. is not new. In fact, such a laboratory of sorts presently exists in the Headquarters Building. When this laboratory was first established a number of years ago, it was thought that it might function in a major way by being of service in furthering the work of the National Formulary Committee and in other areas involving drug standards. This never materialized fully, not because of any unwillingness on the part of the A. Ph. A. staff but largely because of the very limited budget on which it was forced to operate.

At the present time, there are urgent reasons why the A. Ph. A. Laboratory must be revitalized, the staff expanded, and some of the original purposes for having this laboratory fulfilled. For a long time, the A. M. A. laboratory rendered a great service as a neutral and unbiased group responsible to neither industry nor government. This laboratory, however, is no longer functioning although the need for some such service has become even more imperative. Both those responsible for the revision of the Pharmacopeia and those in charge of the National Formulary have innumerable problems relating to drug standards for which laboratory services are absolutely essential. In the past, much of this work has been done voluntarily by laboratories in our colleges and universities. Today, however, some of the techniques and procedures which are required are so time-consuming and so demanding that it has become increasingly difficult to find those capable and willing to do the work which is involved. While it is a high honor for one who is an expert to be chosen as a member of the U. S. P. Revision Committee or the N. F. Committee, it often is an unreasonable thing to expect such an individual to spend day after day in the laboratory carrying out complicated analyses. It is, furthermore, difficult to justify having the cost of such work underwritten by the educational institution where the member of the Committee teaches. Even in those cases where such can be done, the need for some unbiased referee frequently arises, particularly when there is some disagreement between industry and government and the opinion

of a third party is needed. Industry itself is faced with a somewhat similar problem since, while each pharmaceutical company maintains its own laboratory, a suggested assay procedure must be checked by someone else. While the integrity of government laboratories is not questioned and even though there is the closest cooperation between government and industry, a third party is quite essential in making certain that methods as adopted are both valid and workable.

From our viewpoint, it would seem that there are several groups which have a very important stake in the establishment and operation of a non-government, non-industry, impartial laboratory which would be of service to all. These groups are: those responsible for the U. S. P. and the N. F., the pharmaceutical industry, organized pharmacy, and organized medicine. Surely, the establishment of high standards for drugs and medicines is important to all. In surveying the ideal location and operation of such a laboratory, the facilities of the A. Ph. A. would seem to be ideal. The Pharmacopeia Building in New York is not adapted to this; the A. M. A. has given up its role in this direction; and it would seem to be both undesirable and inadvisable for the Pharmaceutical Manufacturers Association to do this on their own.

We strongly urge the revitalization of the A. Ph. A. Laboratory with the needed expansion of both its staff and facilities. We also feel that substantial support for this laboratory is justified and in the interest of the several groups, other than government, who are concerned with drug standards. It is services such as this and the willingness of all groups to support such services financially which justify the continued public confidence and support which our professions and the pharmaceutical industry enjoy. This type of support which is given without thought of financial return would be still further evidence of the social consciousness and high responsibility of which the professions of pharmacy and medicine and the drug industry can justifiably be proud.

L. F. Tice

DRUG EVALUATION

DURING the period from October 1958 to May 1959, a series of lecture and discussion programs devoted to the general theme of CURRENT METHODS OF DRUG EVALUATION was conducted at the Philadelphia College of Pharmacy and Science, under the sponsorship of the Department of Pharmacology. The lectures were presented by researchers, representing several of the pharmaceutical organizations in the New York-Philadelphia area, actively engaged in the complexities of drug evaluation.

The topics selected for consideration sampled currently important aspects of the pharmacologic screening and definitive study of drugs, especially in areas in which considerable controversy exists in regard to choice and validity of methodology. It was not the purpose of this seminar series to attempt a complete survey of the approaches to the analysis of drug action.

Beginning with this issue, the edited transcriptions of the lectures are to be published individually in the *American Journal of Pharmacy*, and will be available in the form of a monograph upon publication of the entire series.

The members of the Department of Pharmacology are grateful to the contributors who gave so generously of their time and talents, and trust that this monograph will be found useful by our colleagues concerned with the multifaceted problems of drug evaluation.

G. VICTOR ROSSI
Director, Department of Pharmacology
Philadelphia College of Pharmacy and Science

November, 1959

EVALUATION OF ANTIHYPERTENSIVE DRUGS*

By Robert A. Maxwell

Research Department, CIBA Pharmaceutical Products, Inc.,
Summit, New Jersey.

CARDIOVASCULAR disease, with its sequelae, arteriosclerosis, renal disease, cerebral hemorrhage, and coronary disease, is the leading cause of death at the present time. As a consequence, the study of the action of drugs on the heart and blood vessels occupies an important place in medical research. At the same time, there is in progress an enormous effort to find synthetic and naturally occurring compounds which would be beneficial in vascular diseases. This has resulted in the development of a group of effective therapeutic agents which have found application in a variety of cardiovascular disorders. We have been deeply involved with cardiovascular work and I should like to discuss an approach to one aspect of the problem—the search for antihypertensive agents—and to expound a little of the philosophy some of us have developed concerning it.

Generally speaking, agents which are useful in the therapy of hypertension have been detected by biological screening tests. In most instances, substances which lower the arterial pressure of hypertensive patients have been screened out and selected because they produce hypotension in the normotensive anesthetized laboratory animal. Therefore, we generally correlate a hypotensive effect in animals with an antihypertensive action in humans and, on a pragmatic basis, we have been justified in doing so.

In both normotensive and hypertensive states, the major mechanical factors involved in producing blood pressure are the following:

I. The pumping action of the heart and the resultant cardiac output;

II. The resistance in the arterial periphery (termed "peripheral resistance");

III. The volume of blood in circulation;

IV. The viscosity of the blood;

V. The elasticity of the arterial walls.

---

* Presented at the Seminar on *Current Methods of Drug Evaluation*, November 1958, Philadelphia College of Pharmacy and Science, Philadelphia 4, Pa.

Antihypertensive and hypotensive drugs generally produce alterations in factors I and II and occasionally in III, if the possibility of pooling or sequestering of blood by drug action is taken into consideration. Changes in IV are to be avoided. Changes in V would be of great value in many hypertensive states; unfortunately, these changes are not yet in the realm of drug action.

Factors I (cardiac output) and II (peripheral resistance) are dependent on the action of involuntary muscle; i.e., on the contractile actions of the heart and blood vessels which in non-pathological states are nicely adjusted to maintain homeostasis by complex neural and humoral mechanisms. By neural mechanisms, we are referring to autonomic reflex arcs. These are typified by those arcs which have their afferent endings in the carotid sinus and aortic arch and their efferent limbs in the vagus nerves and in the sympathetic nerve trunks which ramify in the heart, blood vessels, and adrenal medulla. By humoral mechanisms, we refer to the catecholamines secreted by the adrenal medullae and the variety of hormones and factors known and unknown which are secreted by various organs and affect cardiovascular muscle.

Factors I and II are subject to alterations by several types of drug action: (a) an action on muscle tissue as produced by agents such as acetylcholine, histamine, nitrites, tolazoline (Priscoline®), dibenzylchlorethylamine (Dibenamine®), or phentolamine (Regitine®); (b) interference with reflex circuits on the afferent side as produced by veratrum alkaloids; (c) interference with reflex circuits on the efferent side as produced by ganglionic blocking agents such as hexamethonium (Hexameton®) or chlorisondamine (Ecolid®); (d) interference with sympathetic outflow by action within the central nervous system as produced by reserpine (Serpasil®) and chlorpromazine (Thorazine®).

A Practical Approach

Practical considerations dictate that the chief goal of a pharmaceutical house is to produce clinically useful agents. Many houses have found that a mass production approach is an orderly method and, most likely, given enough compounds and enough time, it will produce results. As in any large-scale scheme, it is preferable to have a simple procedure which will allow for the rapid, if superficial, evaluation of many units. For this reason, acute studies in anesthetized normoten-

sive laboratory mammals are widely used. A routine procedure is to utilize a mammalian species which is easily accessible, such as the dog, cat, or rabbit. The animals are anesthetized and then a superficial artery is cannulated and blood pressure vs. time is recorded with a suitable manometer and recording instrument.

One observes in this type of preparation a variety of hypotensive reactions ranging from the very transient depressor effect produced by histamine and acetylcholine to the long slow decline in blood pressure seen with agents such as reserpine. It is obvious that the action of acetylcholine or histamine, while strongly depressor, is not of sufficient duration to be of practical value. A gradual decline and sustained action are the patterns of activity preferred in clinical practice. Experience has taught us that this long-lasting, gradual onset of action should be accomplished by an intravenous dose of not more than 5 mg./Kg., or preferably by 1 mg./Kg. or less, if it is to rank with currently available agents in terms of potency. When such agents are detected by the screening program, the next step is to obtain a few of the closely related chemical analogs. The most active one or two compounds are tested for activity following oral administration. Activity by the oral route is a necessity if the agent is to have wide clinical application. If no oral activity can be discerned, the compound is shelved. Once it has been established that an agent has adequate potency and duration of action, and is orally active, an intensive search through a very wide gamut of chemical analogs is made in order to obtain the very best activity that can be built into the molecule.

After one compound has been selected as the best which can be made with a reasonable commitment of time and effort, it is then submitted for toxicological studies. At the same time, the pharmacologist can attempt to find, at least in a rudimentary way, the mechanism of action.

One can determine readily if circulatory reflexes are inhibited. If they are, one can determine if this occurs in the sympathetic efferent or afferent pathways or in the central nervous system. Pressure-flow studies will demonstrate whether reduction in cardiac output or relaxation in the periphery or both are involved in the hypotensive action.

When some understanding of the mode of action of the compound is gained, and with sufficient toxicological studies to indicate that the compound is safe, it is then submitted for clinical appraisal. With a

little luck superimposed over a good deal of reliable pharmacological investigation, one can hope for a clinically useful compound. This is the method as we follow it and I think many other pharmaceutical houses follow the same procedure.

Critique and Problems Involved

The method is, frankly speaking, grossly empirical, and of the "shotgun" variety. It is far from an inquisitive, intellectual approach to finding therapeutic agents. Its one real advantage—and an important one, however—is that it produces results; we succeed in developing useful antihypertensive agents. However, with a little thought about this situation, one quickly realizes that the agents discovered by these pharmacological methods are efficacious because they attack those mechanisms which are common to the normotensive and hypertensive states. That is to say, for example, that reduction in cardiac output with concomitant depression of compensatory reflexes will be effective in lowering blood pressure in both normotensive and hypertensive conditions. Thus, we cannot reasonably expect that the method outlined, except by mere chance, will produce a compound which will attack those cardiovascular derangements which are peculiar to the hypertensive state. This fundamental criticism will be brought up again in this discussion. For now, may I turn to an examination of an important problem involved in the method that I have outlined in the previous section, since, regardless of theoretical shortcomings, this method is widely used and of practical interest?

An obvious complicating factor in the usual screening methods is anesthesia. Many people have been bothered by the fact that an anesthetic—in most cases a barbiturate—is used in routine laboratory preparations and wonder what this effect may have on the screening of potential antihypertensives. Could it be possible that anesthesia could mask a hypotensive action in the normotensive animal? A less worrisome possibility, but a real one when one considers the time and effort given to studying a compound, is that anesthesia might lead to false positive evaluations.

It would seem that we should determine whether or not drugs could be better screened in unanesthetized animals. In deciding this question for ourselves, we have limited our research primarily to the use of unanesthetized dogs. We have tried to work with monkeys,

rabbits, and other species and found that the dog, by virtue of its size, docility, and intelligence, lends itself most readily to reliable measurement of blood pressure in the unanesthetized state.

We utilize dogs which are docile in preliminary handling and which have subsequently been given weeks of training. These animals are taught to lie in a supine position on an animal board and to accept femoral arterial puncture calmly. We have found that boxer dogs lend themselves very nicely to these studies.

The apparatus used to perform the punctures is shown in Fig. 1. It is simply a 5 ml. syringe attached to a three-way stopcock onto which is soldered a weighted brass tubing. The weight increases the mass of the apparatus and allows for a stable positioning of the instrument. An ordinary flexible cardiac catheter connects the puncture device to the lead catheter of the Sanborn Electromanometer. A rubber tubing connects a pressure bottle filled with sterile saline to the lead catheter. A pressure of 300 mm. Hg is maintained in the bottle. A needle valve is opened to allow a very, very slow backflow into the puncture apparatus. This prevents clotting in long experiments.

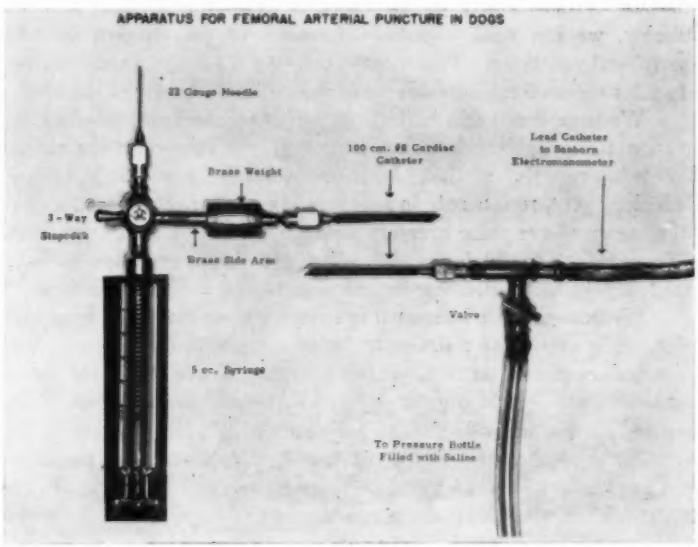

FIG. 1.
Apparatus for performing femoral arterial puncture in the dog.

When the puncture is being made, the valve is turned so that the blood will flow into the syringe as the artery is pierced. With a little experience, it can be determined when one is properly situated by noting the rapidity with which the blood enters the syringe. When a proper puncture is made, the three-way stopcock is turned to open the hydraulic connection to the Sanborn Electromanometer. The instrument we describe is an adaptation of an apparatus which was originally devised by Dameshek and Lohman (1) for use in performing punctures in humans. We have adapted their apparatus so that it can be used for continuous recording of systolic and diastolic pressures in dogs.

We have also utilized another method to gain more information from the unanesthetized dog. By surgically placing one of the carotid arteries into a tube of skin, central pulse contours can be obtained from unanesthetized animals by needle puncture. Using manometers with adequate frequency response, a very high fidelity tracing of the central pulse contour can be obtained. The method of Remington and Hamilton (2) as amended by Remington (3) can then be used for calculating cardiac index. Since the pulse contour is a blood pressure tracing, we can readily make estimations of the changes in total peripheral resistance. This method can be used in the unanesthetized dogs for repeated measurements over hours, days, weeks, or months.

We have found that barbiturate anesthesia will clearly affect the response to ganglionic blocking drugs. In the absence of anesthesia, 320 microgm./Kg. of chlorisondamine chloride, a potent ganglionic blocking agent, results only in a decline of systolic pressure and a clear diminution of the pulse pressure without lowering diastolic pressure. The same animal under pentobarbital anesthesia responds to chlorisondamine with a decrease in both systolic and diastolic pressure.

We became more interested in studying these divergent responses since they were quite a dramatic demonstration of the effects of barbiturate anesthesia on responses to a drug. If one calculates pulses obtained from several dogs, it is found that chlorisondamine markedly reduces cardiac index in the absence of anesthesia but the animals are apparently capable of reflex compensation for this action; therefore, not much effect on mean blood pressure is observed (Fig. 2). In the same animals, the effect of the combination of chlorisondamine and a barbiturate elicits a reduction in index but the animals now apparently cannot compensate, or compensate only partially at best, and a decline in mean pressure ensues (Fig. 2).

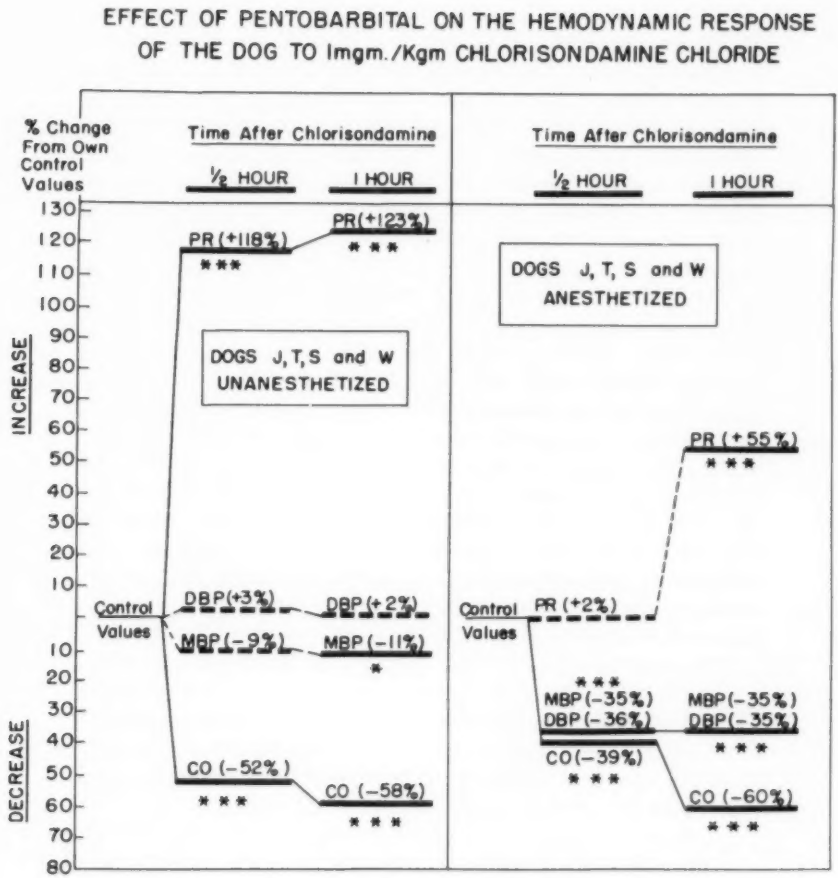

FIG. 2.*

Effect of pentobarbital on the hemodynamic response of the dog to 1 mg./Kg. chlorisondamine chloride. All "unanesthetized values" are in terms of per cent change in each animal from its own unanesthetized controls. All "anesthetized values" are in terms of per cent change of each animal from its own anesthetized controls. CO = cardiac index, PR = peripheral resistance, MBP = mean blood pressure, DBP = diastolic blood pressure, * = significantly different from controls at 5 per cent level, *** = significantly different from controls at 0.1 per cent level, --- = not significantly different.

*Reprinted, with permission, from *J. Pharmacol. Exp. Therap. 123,* 238 (1958).

It seems obvious from this particular study that anesthesia can affect the responses of dogs to drugs. In the case of chlorisondamine, anesthesia permits a hypotension to occur which would not have occurred in the absence of anesthesia. Since ganglionic blocking agents are clinically effective antihypertensives, these facts might be construed as an argument in favor of using anesthetized animals. However, it should be noted that the blocking agent was not without effect in the normotensive unanesthetized dogs. In our experience, in all cases where we have observed hypotension in anesthetized normotensive dogs, detectable changes, if not hypotension *per se*, have been seen in unanesthetized normotensive dogs. A characteristic change is a diminution of pulse pressure. Even more important, cardiovascular effects have been seen in unanesthetized normotensive dogs with agents which did not lower the blood pressure level of anesthetized normotensive dogs (4). Therefore, we would seem to be warranted in saying that, in theory, screening should be carried out in unanesthetized dogs. I think, if it were not for some other factors which I am going to enumerate, it certainly would be a wise thing to do. First, the training and maintenance of a satisfactory number of dogs are factors which, in themselves, are nearly prohibitive. Furthermore, the lethal effects of many unknown compounds, plus humane considerations, necessarily prohibit the wholesale use of unanesthetized animals for routine screening of compounds.

We have found instead that normotensive unanesthetized animals are better utilized for studying the circulatory effects following oral administration of drugs or for studying the circulatory effects of chronic administration of drugs. Unanesthetized animals are also especially useful for comparing drugs since a backlog of information can be built up for many compounds in the same animal.

Likewise, trying to use unanesthetized hypertensive dogs for screening, while in theory the ideal preparation, adds another limitation to the ones that I have just mentioned—that of difficult surgery. One possible practical alternative is to use unanesthetized hypertensive rats which are cheaper and more easily operated and, therefore, more expendable in a mass screening program. This might be a profitable approach for, while it would pick up hypotensive agents, it would also be capable of sorting out agents which are specifically antihypertensive. We have made some use of this approach but have not used it as extensively as perhaps we might. Instead, we have taken another direction.

Another Approach

On the basis of some of our findings with several agents, we have been led to a different theoretical approach. In some recent work, we have discovered that the central nervous system stimulant methylphenidate will block the carotid occlusion reflex. We can see in Fig. 3 the very marked suppressant effect that methylphenidate (Ritalin®) has on the carotid occlusion reflex. Note that this suppression of the reflex occurs when the arterial pressure is relatively unchanged. Another central nervous system stimulant, amphetamine, did not have this blocking effect on the reflex pressor response. Thus, central nervous system stimulant properties were not sufficient to explain the blockade.

Likewise, we found another interesting effect. Methylphenidate completely suppressed the pressor response produced by amphetamine. The effect was very dramatic. If one imposed methylphenidate in the middle of the pressor response elicited by amphetamine, within two or three heart beats, the pressure fell to control levels. Even at high doses of methylphenidate subsequent to amphetamine, the pressure rapidly adjusted to near pre-amphetamine control levels (Fig 3).

Since we were demonstrating two rather unique antihypertensive actions in a normotensive dog, we were interested in trying to determine how these actions were elicited. We eliminated the possibility that methylphenidate exerted a blocking effect in sympathetic efferent pathways by showing that large doses of methylphenidate did not inhibit the contractions of the nictitating membrane evoked by preganglionic faradization of the cervical sympathetic trunk in cats (Fig. 4). We were also able to demonstrate that, in the decentralized nictitating membrane of the cat, methylphenidate antagonized the contracting action of amphetamine. We take this last fact as fairly good evidence that methylphenidate is antagonizing the effect of amphetamine directly in the smooth muscle.

These observations led us to suspect that methylphenidate, while not a hypotensive agent, might display some antihypertensive activity. To test this possibility, methylphenidate was administered to unanesthetized renal hypertensive dogs. Methylphenidate elicited an antihypertensive effect of about ten-minutes' duration (Fig. 5).[1] To

[1] In a recent publication, Darvill (5) has reported an antihypertensive action tor methylphenidate in geriatric patients.

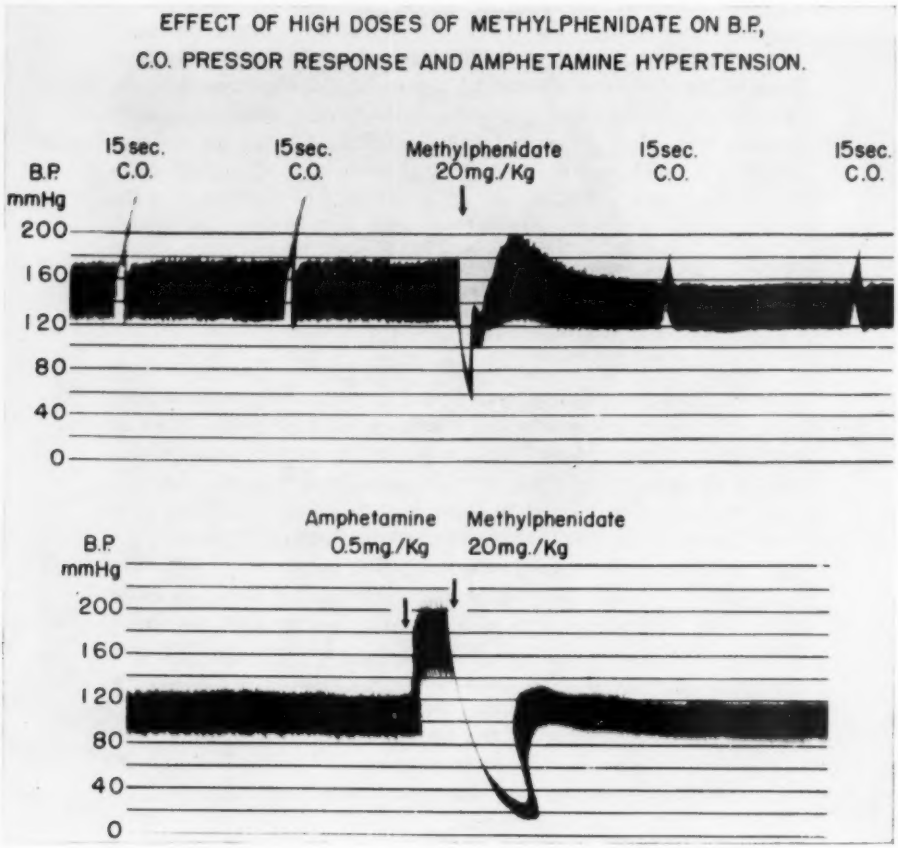

FIG. 3.*

(Upper) The effect of a large intravenous dose of methylphenidate on arterial blood pressure and carotid occlusion reflex pressor responses (CO) in the dog under pentobarbital anesthesia. These blocking effects on CO can be obtained with doses as low as 2 mg./Kg. The large dose of methylphenidate was employed to demonstrate its lack of sustained hypotensive properties.

(Lower) The antagonistic action of a large intravenous dose of methylphenidate and the pressor response elicited by amphetamine. A dose of 4 mg./Kg. intravenously will suppress the action of amphetamine without lowering blood pressure below control levels. Note that, despite the high dose of methylphenidate, the blood pressure quickly recovers to near control levels.

* Reprinted, with permission, from *J. Pharmacol. Exp. Therap. 123, 22* (1958).

show that this antihypertensive action was not due to the central nervous system stimulant properties of methylphenidate, we gave amphetamine to the same dog. Amphetamine elicited only a pressor response (Fig. 5).

These results were highly interesting to us, but the central nervous system stimulant action of methylphenidate obviously prohibits its use as a practical antihypertensive agent. We had to use relatively large doses to produce a modest antihypertension. Nonetheless, we had a demonstration of an agent which had antihypertensive properties but very little hypotensive action.

From all this, we drew the conclusion that, coupled with the search for compounds producing hypotension in the anesthetized normotensive dog, one might profitably look for agents which inhibit pressor drugs or reflex pressor responses while not significantly affecting the mean blood pressure *per se*.

We have used a variety of pressor agents such as norepinephrine, DMPP (1:1-dimethyl-4-phenylpiperazinium iodide), and amphetamine, and the carotid occlusion reflex, and have looked for agents fitting the criteria outlined. It is our feeling that this list of pressor

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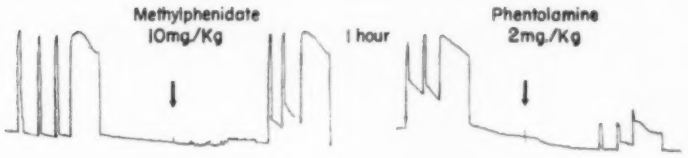
EFFECT OF METHYLPHENIDATE ON CONTRACTIONS* OF THE CAT NICTITATING MEMBRANE



*Spikes produced by 10 sec. @ 2min. pregang. faradization of cerv. symp. trunk.

FIG. 4.*

The lack of effect of intravenous methylphenidate on the contractions of the nictitating membrane elicited by preganglionic faradization of the cervical sympathetic nerve. The ability of phentolamine to prevent the response is also shown for purposes of control.

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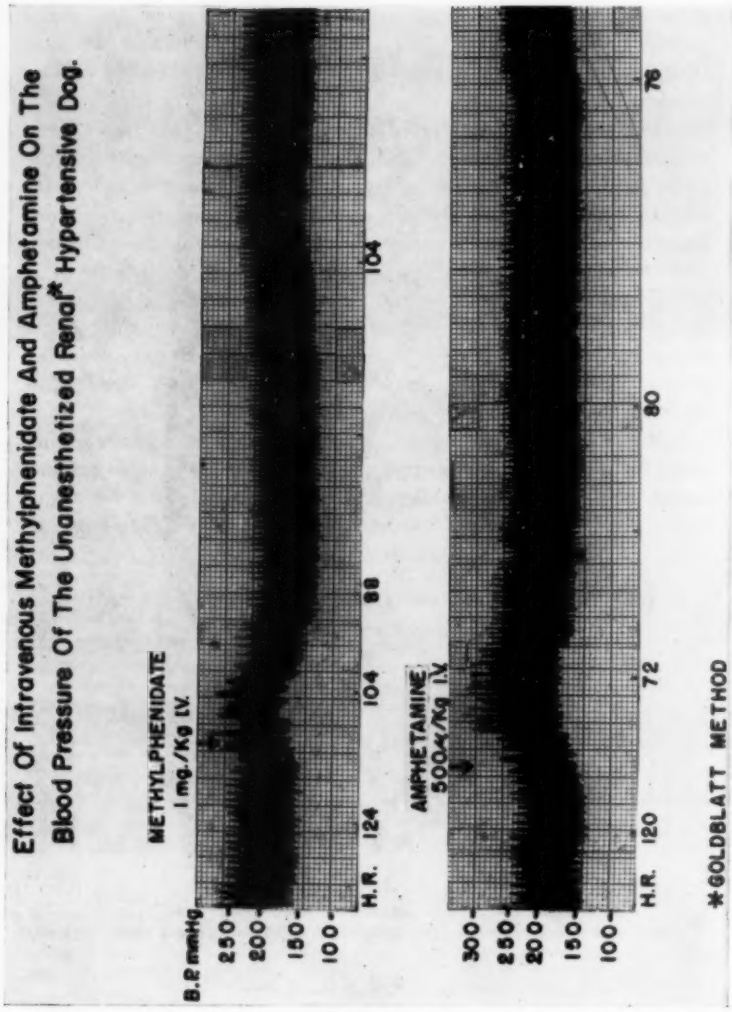
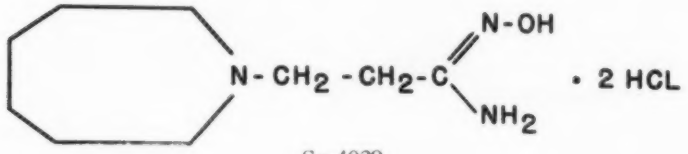


FIG. 5.*

Effect of intravenous methylphenidate and amphetamine on the blood pressure of the unanesthetized renal hypertensive dog. Both records are from the same animal.

*Reprinted, with permission, from *Arch. internat. Pharmacodyn. 112, 26* (1957).

agents should be extended in the future. We have studied one compound which blocked several pressor responses without producing marked hypotension. The compound is hexahydro-1-azepinepropionamidoxime dihydrochloride, more readily known as Su-4029. We found that this agent would markedly suppress amphetamine pressor responses. A single dose of 30 mg./Kg. administered intravenously resulted in a very protracted effect, the duration being approximately four to six weeks (Fig. 6).



Su-4029

I will not labor the reader with the details of the studies we have conducted with Su-4029 since they have been reported elsewhere (4, 6). In summary, our studies concerning Su-4029 demonstrated a potent and protracted antihypertensive action in the unanesthetized renal hypertensive dog and only a relatively insignificant action in the normotensive dog (Fig. 7). We were unable to demonstrate an inhibiting effect of Su-4029 on afferent or efferent sympathetic transmission.

Since we could not demonstrate any of the usual types of autonomic blocking effects for this drug, e.g., adrenergic blockade or ganglionic blocking action, or even a clear cut hypotensive action, we wonder whether an effect of Su-4029 on the smooth muscle could account for its antihypertensive activity. The necessary correlate to this reasoning is that the arteriolar smooth muscle in the hypertensive animal is somehow different from that in the normotensive animal. Whatever Su-4029 does to affect smooth muscle, it is enough to produce an antihypertensive action but it is not sufficient to produce a hypotensive action.

Conclusions

I hope that our efforts and thinking are not misdirected and that we are developing an approach which will allow us to pick out agents which are true antihypertensives. Looking for agents which will

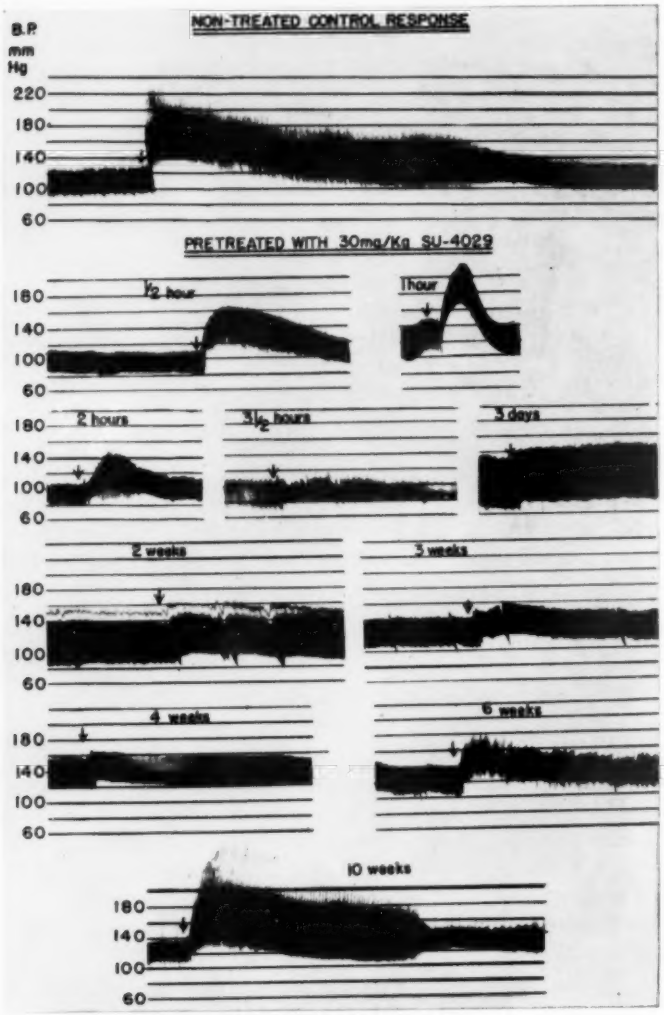


FIG. 6.*

Time course of inhibition of amphetamine-induced hypertension by Su-4029 in the normotensive anesthetized dog. Time notations refer to time elapsed after a single intravenous injection of Su-4029. Five-tenths mg./Kg. of amphetanime sulfate administered intravenously at arrows.

* Reprinted, with permission, from *J. Pharmacol. Exp. Therap. 123,* 128 (1958).

suppress pressor actions but at the same time will not lower arterial blood pressure in the normotensive dog may be a method that will yield good results.

In the way of general conclusions, I would like to note that there are now a relatively large number of useful hypotensive agents. All have side effects and do not specifically treat those factors peculiar to the hypertensive state since their effects are also demonstrable in normotensive animals. While occupied with finding better, more useful hypotensive compounds, a fruitful endeavor would be a search to find true antihypertensive agents and, while our present methods are obviously limited and sketchy, they do not rule out the possibility of doing this.

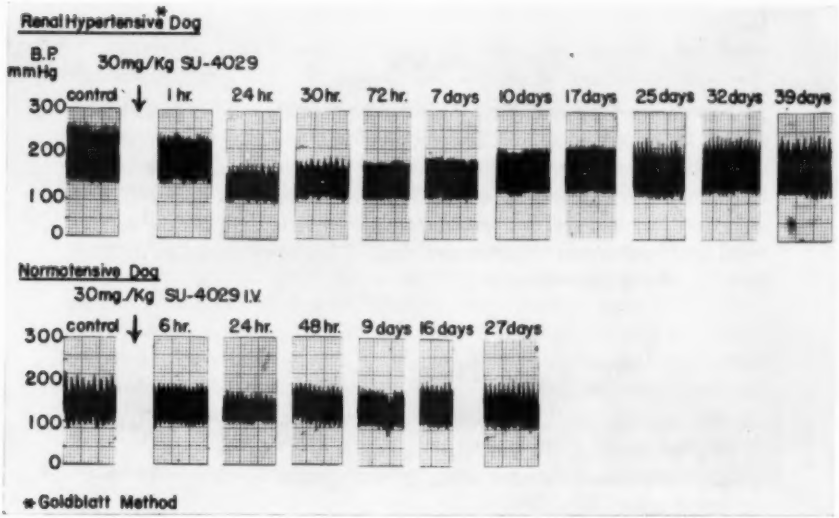


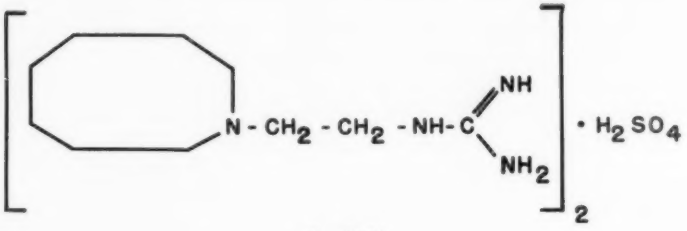
FIG. 7.*

Effect of Su-4029 on the blood pressure of unanesthetized renal hypertensive and normotensive dogs. Time notations refer to time elapsed after a single intravenous injection of Su-4029.

* Reprinted, with permission, from *J. Pharmacol. Exp. Therap. 123,* 128 (1958).

Addendum

Since delivering this discussion, Su-4029 has received clinical trial both here and in Europe. The compound produces antihypertensive actions particularly of the orthostatic type. In studying analogs of Su-4029, we have discovered Su-5864 which is:



Su-5864

[2-(octahydro-1-azocinyl)-ethyl]-guanidine sulfate, and is generically known as guanethidine. This compound has many of the properties of Su-4029 and a few peculiar to itself. Specific to our point is the fact that this compound is not markedly hypotensive in normotensive dogs but has marked and protracted antihypertensive action in the renal and neurogenic hypertensive dog. This compound has to date been successful in the clinics (7, 8).

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NEW NITROGEN MUSTARDS IN THE CONTROL OF LEUKEMIA

By John R. Sampey *

NITROGEN mustards have been the most frequently employed agents in the management of leukemia during the last decade (35). Methyl-bis(β-chloroethyl)amine, or *HN2*; methyl-tris(β-chloroethyl(amine, or *HN3*; and methyl-bis(β-chloronaphthyl)amine, or R48, have been the most used chemicals in this therapy. A review of the new nitrogen mustard, chlorambucil, or CB1348, has recently been made on more than 500 patients with leukemia (36). The present study presents current clinical trials with several other new N-mustards.

Nitrogen Mustard Oxide

Methyl-bis(β-chloroethyl)amine-N-oxide, or nitromin, has been the subject of a score of clinical investigations, mostly by Japanese scientists, on the control of leukemia. In 1952-54 (21, 22) Kimura and associates reported good to fair clinical and hematologic remissions in five chronic and three acute cases of leukemia out of twelve patients treated, and they observed fewer undesirable side-effects than with the older N-mustards. Kawakita *et al.* (19) in 1953 described four clinical and one hematologic remission in five patients with chronic myelocytic leukemia, and a hematologic remission in one patient with erythroleukemia, but no improvement in the bone marrow after nitromin therapy. The following year (20), he and associates recorded some response in two patients with chronic myelocytic leukemia, one with acute myelocytic leukemia, and one with subacute lymphocytic leukemia given nitromin orally. Koyama *et al.* conducted two investigations with N-mustard oxide: in 1953 (23), they noted some hematologic response in three patients with chronic myelocytic leukemia, but the toxic effects were bad; in 1958 (24), they reported that 15 of 25 cases of chronic myelocytic leukemia showed objective signs of improvement, and that three of 23 patients with acute leukemia gave objective evidence of remissions. In 1953, Hirota (16) described a brief, partial response in one patient with acute aleukemic myeloid leukemia after therapy with nitromin, vitamin B_{12}, teropterin,

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and transfusions; and Nakamura (28) administered nitromin, urethan, and transfusions in one patient with subacute erythroleukemia to induce a brief remission. Kuroyanagi (25) in 1953 observed seven months' good clinical and hematologic remission in a patient with chronic myelocytic leukemia after nitromin therapy.

In 1954-55, Consoli conducted several clinical trials of nitromin: in one study (5) he noted little effect in two patients with acute leukemia, and a good hematologic remission in one case of chronic myelocytic leukemia; in another investigation (6) he described good remissions in four cases of chronic myelocytic leukemia and less response in one case of chronic lymphocytic leukemia and three cases of istioleukemia; in 1955 (7), he continued his clinical trials with nitromin on four cases of chronic myeloid, one chronic lymphoid, and three acute leukemic cases, observing little effect in the latter. Nakauchi (29) obtained a hematologic remission in a patient with subacute myelocytic leukemia who received concomitantly nitromin and the dye lumin, while Nasr and Awad (30) observed no benefit from nitromin therapy in one case of chronic lymphocytic leukemia.

During 1955, Farber (13) reported no benefit from nitromin therapy of single cases of acute leukemia, Hodgkin's disease, Wilms' tumor, etc. In 1956, Lovisetto *et al.* (26) recorded a good remission in one case of chronic lymphocytic leukemia, fair to good remissions in three chronic myelocytic leukemias, and no response in one acute case. Dudik (10) noted good subjective response in one patient with subacute myelocytic leukemia after nitromin therapy, but the leukopenic reaction was strong.

In 1957, Hörlin and Schmitt (17) induced one good and one fair remission in seven patients with chronic myelocytic leukemia and a fair response in one chronic lymphocytic leukemia, but no effect was observed in two patients with acute myelocytic leukemia. Apel and Klages (2) observed several remissions, one lasting eight months, in three patients with chronic myelocytic and three with chronic lymphocytic leukemia following N-mustard oxide therapy. In 1958, Eckhardt *et al.* (11) reported an objective response in one of two patients with lymphocytic leukemia.

Degranol

Bis-(β-chloroethyl)amino-D-mannitoldichlorhydrate, or BCM, or degranol, has been employed in the control of scores of cases of

leukemia. In 1956, Sellei *et al.* made two studies on the use of degranol: in one (38), they treated 39 patients with lymphocytic leukemia and 14 with myelocytic leukemia, and described subjective clinical response; in the other investigation (37), they observed that six of seven patients with chronic lymphocytic leukemia had complete clinical and hematologic remissions for several months, and that three of six cases of chronic myelocytic leukemia had good remissions and three, only fair responses; they observed also reduction of hemorrhages in two of four acute cases after the use of degranol. In 1958 (39), their tabulations on BCM therapy were even more impressive: 31 of 35 cases of chronic lymphocytic leukemia had complete remissions for three months, with 17 lasting for 24 months; 14 of 18 chronic myelocytic leukemia had complete remissions for three months, with five lasting to 24 months; and five of 10 patients with acute paramyeloblastic leukemia had remissions for three months, with two going to six months. In 1958, Eckhardt *et al.* (12) reported 17 of 35 patients with chronic lymphocytic leukemia had complete remissions to two years, and 18 had a fair response for a brief period; they also described some remissions in cases of acute leukemia extending for six to eight months, but complicated by leukopenia and thrombopenia. Szentklaray (41) employed a combination of degranol and vitamin C to induce 12 objective and subjective responses in 12 patients with chronic lymphocytic leukemia, and four good remissions and one fair objective remission in six cases of chronic myelocytic leukemia. Zulik (43) recorded good hematologic remissions in four of five patients with chronic lymphocytic leukemia, and some hematologic remission in one patient with acute myelocytic leukemia, but no response in two patients with chronic myelocytic leukemia. Benko (3) brought about some improvement in one patient with chronic lymphocytic leukemia with transfusions and BCM, while Papac *et al.* (32) noted a remission in one case of chronic granulocytic leukemia with BCM.

N-Mustard Phosphoramide Esters

Brichta *et al.* (4) employed B518 to lower the leukocyte count in five patients with chronic lymphocytic leukemia, but they judged the results poor, for there was no change in the bone marrow or granulocyte/lymphocyte ratio. Gross and Lambers made two clinical studies with N-mustard phosphoramide esters: in one (14), they noted

a fair response in three of seven patients with chronic myelocytic leukemia, and in the other (15) they observed a fair response in all seven patients with chronic myelocytic leukemia following the administration of N,N-bis(β-chloroethyl)-N′,o-propylendiamide ester of phosphoric acid, or Endoxan.

Phenylalanine Mustards

Consoli used DL-p-bis(β-chloroethyl)amine-phenylalanine, or Sarcolysin, in two investigations of chronic myelocytic leukemia: in one, he and Violante (9) secured a good remission and, in the other, he (8) noted only a fair response in one patient. Loviesetta and Castellano (27) induced good remissions in all three patients with chronic myelocytic leukemia, but only two of five patients with chronic lymphocytic leukemia had good remissions with Sarcolysin. Papac *et al.* (31) failed to obtain a response in treating one patient with acute leukemia with p-di-2-chloroethyl-amino-L-phenylalanine, or CB3025.

Uracil Mustards

4-Methyl-5-(bis-β-chloroethyl)amino-uracil, or Dopan, induced good hematologic remissions and reduction in the size of the spleen in six of seven patients with chronic myelocytic leukemia, the improvement lasting to 18 months, according to Vishnyakova (42). Shanbron *et al.* (40) employed 5-bis(β-chloroethyl)amino-uracil, or U8344, on 14 chronic granulocytic cases and 11 chronic lymphocytic leukemia patients to induce the best response of any hematologic disorders these investigators tested.

Sulfur Mustard

In two publications, Petrakis *et al.* followed the action of 1,2-bis-(β-chloroethylthio)ethane, or SM-1, on leukemia: in a preliminary trial (33) they tested this agent on four patients with acute leukemia, but observed better results in Hodgkin's disease and lymphosarcoma; a year later (34) they concluded that SM-1 gave no response in two patients with acute lymphocytic leukemia, or four with chronic lymphocytic leukemia, or one with chronic granulocytic leukemia. Alpert (1) noted some response in patients with chronic lymphocytic leukemia after sulfur mustard therapy.

N-Mustards Related to Chloroquine and Quinacrine

Analogs of these antimalarial drugs were effective in patients with chronic leukemia in preliminary tests of Jones and associates (18).

Summary

The results of this study on the control of leukemia with the newer N-mustards are summarized in Table I. It should be noted that several clinical reports failed to record the number of patients treated and/or the number responding, and that the new mustard, CB1348, has been the subject of an earlier study (36).

TABLE I

CONTROL OF LEUKEMIA WITH NEW N-MUSTARDS

N-Mustard	*Cases*	*Good Remissions*	*Fair Remissions*
Nitromin	121	13	55
Degranol	196	79	44
N-mustard Phosphoramide Ester	23	—	15
Phenylalanine Mustards	11	6	1
Uracil Mustards	32	6	—
SM-1	11	—	4
Chloroquine, Quinacrine Compds.	—	—	—

Acknowledgments

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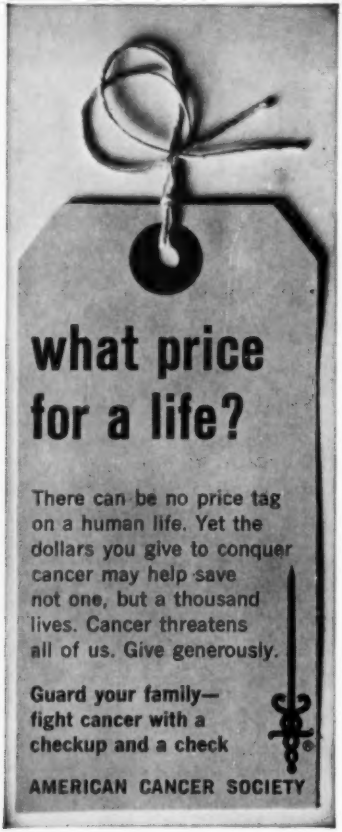
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